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An Alternative Synthesis of Cycloalkyl-Substituted CPA Catalysts and Application in Asymmetric Protonation Reactions**

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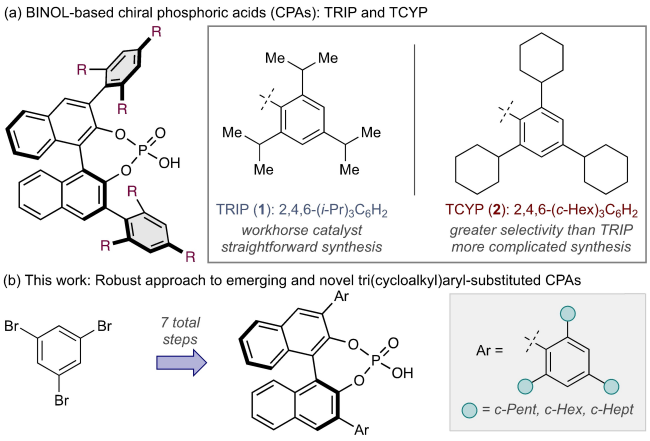
An alternative synthesis of cycloalkyl-substituted CPA catalysts is reported. A Negishi coupling offers improved yields and purity of the necessary 1,3,5-tri(cycloalkyl)benzenes. Limitations in the use of commercial organozinc reagents have been identified and a robust procedure for the preparation of these reagents is detailed. Similarly, a robust procedure for the key Kumada coupling is also provided. The route is demonstrated by preparation of three different tri(cycloalkyl)aryl-substituted CPAs and the utility of these catalysts in asymmetric protonation reactions is shown.

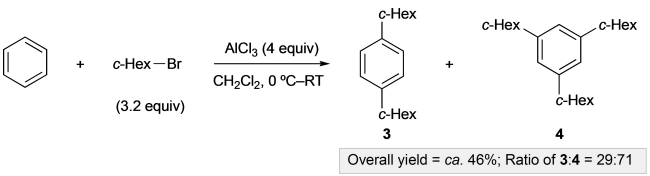
BINOL-derived chiral phosphoric acids (CPAs) are privileged catalysts for a broad range of asymmetric reactions (Scheme 1a).[1] Of this class, the 3,3′-di(2,4,6-triisopropylphenyl)-substituted phosphoric acid **1** (TRIP) has become a workhorse, delivering excellent yields and enantioinduction across a range of asymmetric transformations including 1,2-additions,[2] rearrangements,[3] and reductive aminations,[4] amongst others.[5] More recently, the TRIP analogue TCYP (**2**) has emerged[6] and shown increased selectivity in a series of recent asymmetric transformations including aminations,[7] dynamic kinetic resolutions,[8] and borylation.[9]

The synthesis of **1** is well-documented;[10] however, there are few procedures for the preparation of **2**.[11] In recent work in our group, we found some difficulty in synthesis of **2** and sought to overcome these problems. Here we report the development of an alternative synthetic approach to **2** and other novel tri(cycloalkyl)aryl CPAs (Scheme 1b). We also compare the effectiveness of these catalysts in asymmetric protonation reactions.[12]

Existing approaches to **2** are based upon synthetic access to 1,3,5-tri(cyclohexyl)benzene **4** via Friedel-Crafts alkylation of benzene (Scheme 2).[13]



Scheme 1. (a) BINOL-derived CPAs. (b) This work: An alternative approach to tri(cycloalkyl)aryl-substituted CPAs.



Scheme 2. The issue with a Friedel-Crafts approach to tri(cycloalkyl) benzenes.

While this process does allow access to **4**, we found the reaction to produce mixtures of **3** and **4** in moderate overall yield.[14] Purification by distillation is possible but tedious, and often requires several distillations to increase purity to a satisfactory level. This process also does not allow general access to other 1,3,5-tri(cycloalkyl)benzenes, such as the cycloheptyl variant.

We therefore proposed an alternative and straightforward approach to circumvent this issue based on exhaustive Negishi coupling of 1,3,5-tribromobenzene (Scheme 3a).

Initial experiments using commercial organozinc reagents (*c*-hexylzinc bromide and *c*-pentylzinc bromide; not shown) were unsuccessful – no product was observed. However, use of the organozinc reagents prepared in house by transmetalation from the Grignard reagent (also prepared in house) delivered the tri(cycloalkyl)benzene products **4**, **6**, and **7** in good yield at first attempt. The origin of the difficulty experienced with the commercial reagents is currently unexplained.

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[**] *CPA = chiral phosphoric acids.*

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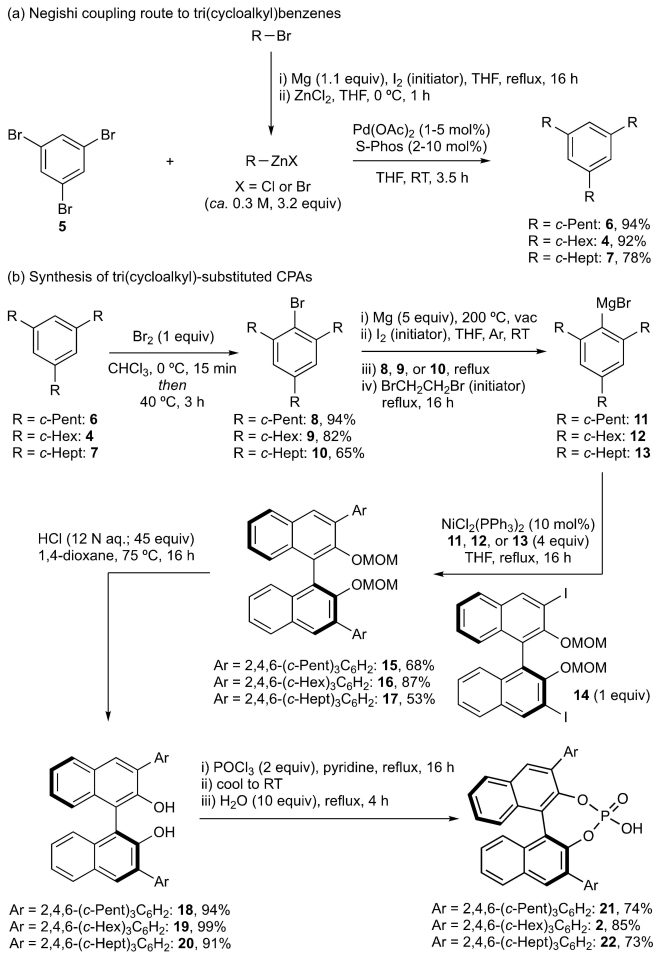


Scheme 3. Improved synthesis of tri(cycloalkyl)aryl-substituted CPAs.

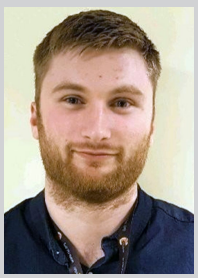
With access to **4**, **6**, and **7**, synthesis of the desired tri(cycloalkyl)aryl CPAs was relatively straightforward (Scheme 3b).[11] Bromination using Br_2 delivered 1-bromo-2,4,6-(tricycloalkyl)benzenes **8**–**10**. Literature procedures for the Kumada coupling of the Grignard reagents derived from **8**–**10** proved problematic:[15] Mg insertion was found to be difficult and irreproducible. Investigation and optimization of this process provided a multi-step but ultimately reproducible procedure where Mg is first heated at 200 °C for 16 h followed by treatment with catalytic I_2 in THF. The aryl bromide is introduced, and the mixture refluxed in the presence of 1,2-dibromoethane as a further Mg activator. Use of Grignard reagents **11**–**13** in the exhaustive Ni-catalyzed Kumada coupling with MOM-protected 3,3′-diodo-BINOL derivative **14** provided reproducible access to the required carbon skeletons (**15**-**17**) of the tri(cycloalkyl)aryl CPAs in moderate to good yield. It was interesting to note that the equivalent Kumada coupling of methoxy-protected 3,3′-diodo-BINOL was entirely unsuccessful.

Deprotection and phosphorylation using literature procedures was straightforward and ultimately provided access to the desired known CPAs **2** and **21**, and the novel *c*-heptyl derivative **22**.

To compare the utility of these CPAs, we assessed their performance in exemplar asymmetric protonation reactions (Scheme 4).[12,16]

The performance of catalysts **2**, **21**, and **22** in the asymmetric protonation reaction to form tertiary carbon centers (Scheme 4a) was broadly similar to the performance using **1** (75%, 97:3 e.r. at −20 °C)[12a] for catalysts **2** and **22**; however, catalyst **21** delivered significantly poorer asymmetric induction. Similar performance of **21** was noted in the related asymmetric protonation reaction to deliver fluorinated stereocentres, where **21** was considerably less selective than using **1** (82%, 96:4 e.r. at −10 °C).[12b] Catalysts **2** and **22** were unreactive at −10 °C; however, these were found to deliver comparable asymmetric induction as **1** at room temperature allowing significantly improved reaction times in this process.

In summary, we have reported an alternative synthesis of tri(cycloalkyl)aryl-substituted CPAs, based on a Negishi coupling route to the central tri(cycloalkyl)benzenes. Optimization of a troublesome Grignard formation and Kumada coupling to forge the carbon skeleton was essential to this route. This approach provided access to a key CPA catalyst (TCYP) and the novel *c*-heptyl derivative. These catalysts are effective in exemplar asymmetric protonation reactions and offer opportunities for reaction development at more convenient temperatures.[17]



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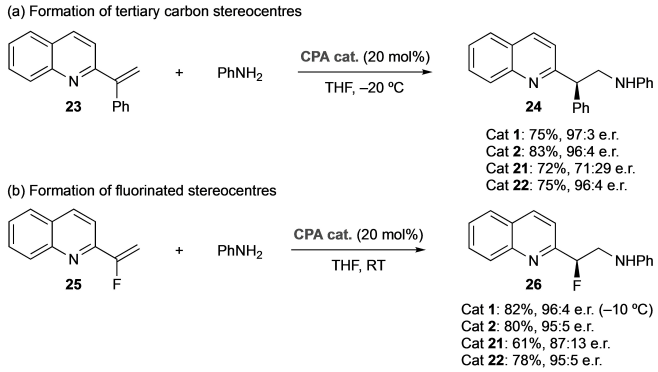
Allan Watson also hails from Glasgow, Scotland, and obtained his MSc degree and PhD from the University of Strathclyde. He then moved to Princeton University as a Lindemann Trust Fellow to work with Professor David MacMillan. He returned to the UK in 2010 to take up an industrial postdoctoral position at GlaxoSmithKline before starting his independent career at the University of Strathclyde in 2011. He moved to the University of St Andrews in 2018. His research interests are based around the development and understanding of catalytic reactions and their application in medicinal chemistry and agrochemistry.



Scheme 4. Application of the tri(cycloalkyl)aryl-substituted CPAs in exemplar asymmetric protonation reactions.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Asymmetric protonation · Brønsted acid · Catalysis · Cross-coupling · Enantioselectivity

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[17] The research data supporting this publication can be accessed at https://doi.org/10.17630/2d4dea0c-af38-4102-8dc9-684f5e6ab525.

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